Comparison of embolization protection device-specific technical difficulties during carotid artery stenting

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Background: **Embolic protection devices (EPDs) consisting of an internal carotid artery (ICA) filter or balloon occlusion are typically used during carotid artery stenting (CAS). This study compares the technical difficulties encountered using these two types of EPD.**

Methods: **A retrospective review was conducted of patients undergoing CAS using a balloon occlusion EPD (balloon group: PercuSurge GuardWire) or filter EPD (filter group: Accunet, AngioGuard, or FilterWire). Complications were defined as minor stroke, National Institutes of Health (NIH) stroke scale <3; major stroke, NIH stroke scale ≥3; transient ischemic attack (TIA), reversible focal neurologic impairment; technical, reversible neurologic compromise during EPD deployment, inability to cross lesion, ICA spasm requiring treatment, EPD-related factors that prolonged CAS.**

Results: **CAS (n = 141) was performed in 133 patients (82% men) with a mean age of 72 of years. Comorbidities included diabetes, 35%; coronary artery disease, 75%; hypertension, 82%; and renal insufficiency, 15%. Indication was previous cerebrovascular accident in 10%, TIA in 29%, and asymptomatic >80% stenosis in 61%. Primary lesions were treated in 83% vs restenosis in 17%. The 30-day event rate was 1.4% major stroke, 2.1% minor stoke, 1.4% myocardial infarction, and 0.7% death. The overall combined 30-day stroke, death, and myocardial infarction rate was 5.6%. The 30-day stroke and death rate was 4.0% in the balloon group (n = 99) and 4.6% in the filter group (n = 42, $P = .51$). EPD-related technical difficulties occurred in 15% of the balloon group and 31% of the filter group ($P < .05$). Technical difficulties included a 10% incidence of reversible neurologic compromise during balloon deployment compared with 0% in the filter group ($P = .002$) and 12% incidence of inability to cross the lesion before predilation in the filter group compared with 0% in the balloon group ($P = .001$).**

Conclusions: **During CAS, both balloon occlusion and filter devices provide acceptable results and appear complimentary. Filters can be used preferentially to avoid a 10% incidence of reversible neurologic compromise associated with balloon occlusion, except in critically narrowed or tortuous lesions when balloon occlusion may be preferred because of a 12% need for unprotected predilatation with filters. (J Vasc Surg 2006;44:56-61.)**

Carotid artery stenting (CAS) has become an accepted alternative to carotid endarterectomy (CEA) for the treatment of obstructive extracranial carotid artery occlusive disease in selected high-risk patients.[1] A major concern is the risk of atheroembolic material released from the carotid plaque during CAS.[2] Initial use of CAS was hindered by an increased incidence of neurologic complications and stroke compared with CEA.[3] In several series, which were largely performed without the use of any cerebral protection, stroke rates were >10%.[4,5]

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The development and subsequent introduction of embolic protection devices (EPDs) has resulted in a decreased rate of stroke after CAS.[1,6,7] Thus, the use of EPDs during CAS is now routine. At present, the three different classes of EPDs are (1) balloon occlusion EPDs that require occlusion of the ICA during CAS, (2) filter EPDs that rely on a filter in the distal internal carotid artery (ICA) to capture atheroembolic particles released during CAS while permitting antegrade cerebral perfusion, and (3) flow reversal/cessation devices that use common carotid balloon occlusion to promote retrograde or no flow in the ICA during CAS.[8-10] Retrograde and flow cessation techniques are promising but have not yet gained widespread clinical use compared with the balloon occlusion and filter EPDs as they remain investigational at this time.[8-10]

Although many types of EPDs exist, all with theoretical advantages and disadvantages, few comparative studies have confirmed or identified any unique advantages or roles that specific EPDs may have in CAS. Because of the dramatic differences in EPD design, it is likely that there are anatomic situations in which individual EPDs may be better suited to prevent stroke during CAS. The purpose of this

study was to contrast outcomes and technical difficulties encountered with balloon occlusion and filter EPDs.

METHODS

The records of all patients treated with CAS for extracranial carotid bifurcation occlusive disease from the first patient treated in December 2002 through September 2005 were reviewed. Excluded were patients who had stent-graft placement for trauma (n = 3), stents placed at the time of CEA for distal flap (n = 4), combined coronary artery bypass grafting and CAS (n = 1), and patients in whom CAS was performed before the availability of EPDs (n = 4). The data had been prospectively entered into a database. This review was approved by the institutional review board.

For purposes of this review, high-risk patients were classified as having either anatomic high risk or medical high risk. Anatomic high risk included 44 patients with previous carotid surgery, neck dissection, radiation therapy to the neck, lesions extending above the C2 vertebral body, presence of a neck stoma, or contralateral cranial nerve injury. Medical high risk (n = 75) included cardiac comorbidity, defined as myocardial infarction (MI) or congestive heart failure ≤3 months, or unreconstructed severe coronary artery disease, and pulmonary comorbidity that required home oxygen. Initially, only high-risk patients were offered CAS, but with increased experience, this procedure was offered to 22 normal-risk patients.

Patients received either 1 week of clopidogrel (75 mg daily) before the procedure or a single 300-mg loading dose of clopidogrel the morning of the procedure. In addition, patients were maintained on oral aspirin indefinitely and clopidogrel (Bristol-Myers Squibb, New York, NY) for a least 1 month after the procedure. Our CAS technique has been previously described in detail.[6] Carotid duplex scanning was performed at 1 day, 1 month, 6 months, and yearly thereafter.

An independent neurologist examined 40 patients who were enrolled in clinical trials. The 101 patients not enrolled in a clinical trial underwent a neurologic examination by the general surgery chief resident or vascular fellow plus the surgical attending on postoperative day 1 and at each clinic visit. An independent neurologic assessment was conducted in 75% patients treated with filters as part of a clinical trial, but only 25% of balloon-treated patients underwent independent neurologic assessment.

Patients with any new neurologic deficit were scored using the National Institutes of Health (NIH) stroke scale.[6] A major stroke was defined as a new neurologic event that lasted >24 hours and had an increase in the NIH stroke scale of >3. A minor stroke was defined as a new neurologic event that lasted >24 hours and was associated with an increase in the NIH stroke scale of ≤3. A transient ischemic attack (TIA) was defined as a new neurologic deficit that lasted <24 hours.

MI was defined as an elevated troponin T level >0.03 ng/mL or an abnormal postoperative electrocardiogram consistent with new MI.

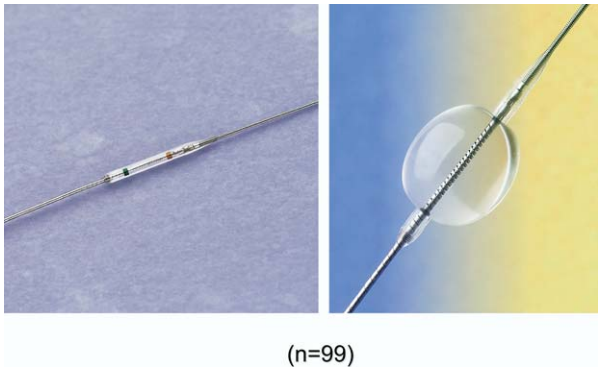

Fig 1. The 99 patients in the balloon group received a GuardWire embolic protection device.

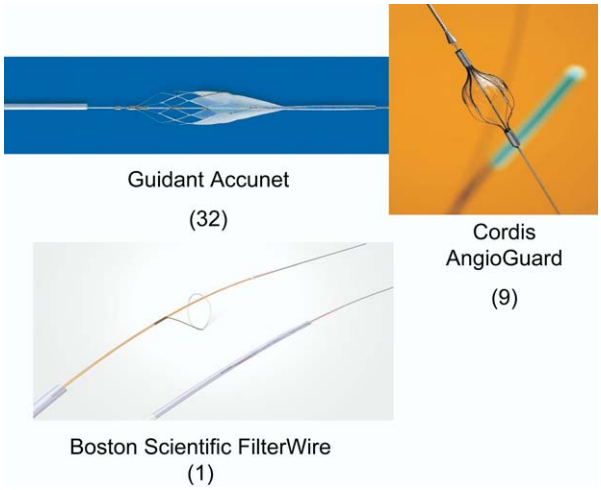

Fig 2. Patients in the filter group received the Accunet, AngioGuard, or FilterWire filter embolic protection devices.

Blood pressure control complications were defined as the need to use intravenous vasoactive medication to lower or raise the blood pressure in a monitored setting after CAS. The blood pressure goals for each patient were different and determined by previous blood pressure, presence of intracranial occlusive disease, and severity of the stenosis treated.

Technical difficulty was defined as neurologic compromise during EPD deployment, inability to cross the ICA lesion with the EPD without predilation, ICA spasm requiring pharmacologic treatment, and any EPD-related event outside of the typical CAS procedure that prolonged the CAS procedure. A transient neurologic deficit that developed during inflation of the embolization protection balloon or with deployment of the filter that completely resolved with deflation of the balloon or filter capture was not considered to be a TIA. This was considered a technical difficulty with use of the EPD and was defined as reversible neurologic compromise.

Table I. Patient demographics

	Filter (n = 42)	*Balloon (n = 99)*	P
Mean age (years)	71	73	.27
Male	74%	89%	.02
Diabetic	29%	35%	.54
CAD	24%	25%	.95
Tobacco*	73%	81%	.54
ACE	62%	67%	.63
Statin	67%	74%	.83
HTN	80%	79%	.34

CAD, Coronary artery disease; *ACE,* angiotensin converting enzyme inhibitor; *HTN,* hypertension.
*Present tobacco use or within past 2 years.

Table II. Lesion presentation of patients in the study groups

	Filter (n = 42) (%)	*Balloon (n = 99) (%)*	P
Asymptomatic	64	60	.45
TIA	29	29	
CVA	7	11	
Primary lesion	74	89	.05
Restenosis	26	11	
Anatomic risk	38	23	.21
Medical risk	38	49	.31

TIA, Transient ischemic attack; *CVA,* cerebrovascular accident.

Inability to cross the lesion with the EPD or inability to cross the lesion only after unprotected predilation was considered an EPD-related technical difficulty and was recorded for both types of EPD. Spasm was defined as ICA narrowing in a previously normal portion of the carotid artery above the stent.

The initial 90 patients treated in the study underwent CAS using the GuardWire PercuSurge EPD (Medtronic, Santa Rosa, Calif). Subsequent patients were enrolled in clinical trials, either CREST (Carotid Revascularization Endarterectomy vs. Stent Trial) (NIH/Guidant) or ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (Cordis), and received the corresponding filter device. Upon Food and Drug Administration (FDA) approval of the Guidant Accunet Filter, surgeon preference also factored into which EPD device was chosen. Patients receiving a GuardWire EPD (Fig 1) during CAS (balloon group) were compared with patients receiving filter EPDs (filter group), which included Accunet (Guidant, Indianapolis, Ind), AngioGuard (Cordis, Warren, NJ), and FilterWire (Boston Scientific, Natick, Mass) (Fig 2). The variables compared between the two groups included incidence of stroke, death, myocardial infarction, and technical difficulties experienced with the use of the two types of EPD.

Data are presented as the mean ± standard error of the mean. Statistical analysis was performed using analysis of variance with post hoc *t* test or χ^2, where appropriate, using StatView Software (SAS Institute Inc, Carey, NC).

Table III. Thirty-day perioperative outcome

	Filter (n = 42) (%)	*Balloon (n = 99) (%)*	P
Major stroke	2.3	1.0	.51
Minor stroke	2.3	2.0	.82
TIA	0	1.0	.73
MI	0	2.0	.56
Reperfusion	0	2.0	.56
BP control	9.5	5	.63
Seizure	2.3	2.0	.82

TIA, Transient ischemic attack; *MI,* myocardial infarction; *BP,* blood pressure control requiring pressors.

Table IV. Technical complications

	Filter (n = 42) (%)	*Balloon (n = 99) (%)*	P
Neurologic comp	0	10	.002
Unable to cross lesion	12	0	.001
Filter clogged	5	0	.07
ICA spasm	12	2	.002
Malpositioned stent	0	2	.56
Other*	7	1	.16

ICA, Internal carotid artery.
*3 cases of delayed retrieval of filter and one case of balloon wire kinking

RESULTS

During the described time period, 141 CAS procedures were performed in 133 patients at Dartmouth Hitchcock Medical Center and the White River Junction VA Hospital. Patients were a mean age of 72 years (82% men). Comorbidities included diabetes in 35%, coronary artery disease in 75%, hypertension in 82%, and renal insufficiency in 15%. Indication was previous cerebrovascular accident in 10%, TIA in 29%, and asymptomatic >80% stenosis in 61%. Primary lesions were treated in 83% vs restenosis in 17%.

Balloon occlusion protection was used in 99 procedures and filter protection in 42 procedures. The patient characteristics for the balloon and filter groups are summarized in Table I. No significant differences were noted between the two groups with the exception of an increased number of men in the balloon group. As shown in Table II, there was no difference in symptoms at presentation between the two groups. However, more patients in the filter group were treated for restenosis compared with the balloon group ($P < .05$).

For the entire cohort, the 30-day event rate was 1.4% major stroke, 2.1% minor stoke, 1.4% MI, and 0.7% death. No intracranial embolization occurred during or immediately after CAS. All strokes occurred between 2 and 12 hours after the procedure. There were no instances of embolization to the proximal M1-2, A1-2 segments as determined by arteriography or computed tomography arteriography. All cases of stroke appeared to be a result of distal microembolization. The overall combined 30-day stroke, death, and MI rate was 5.6%.

The balloon group and filter group had a similar incidence of minor stroke, major stroke, MI, or death (Table III), EPD-related technical difficulties occurred in 15% of the balloon group and 31% of the filter group ($P < .05$). These difficulties are detailed in Table IV. Technical difficulties were EPD specific. No correlation was found between EPD-related technical difficulties and adverse neurologic outcomes after CAS.

Transient neurologic compromise occurred in 10% of the balloon group while the balloon was deployed but did not occur in the filter group ($P = .002$). In eight of ten cases, neurologic changes occurred within several minutes after inflation of the PercuSurge, the other two occurred during bradyarrhythmia after post-stent balloon dilation. All patients presented with global symptoms. In most cases, the procedure was completed by deflating the balloon and then increasing the mean arterial pressure by 20 to 25 mm Hg above baseline. After this maneuver, eight of the ten patients tolerated reinflation of the balloon EPD and stent placement was completed. Two patients who could not tolerate balloon EPD were treated with a filter device (n = 1) or CEA (n = 1). Multivariate analysis did not identify any predictors of failure to tolerate balloon EPD deployment. This included the presence of contralateral ICA stenosis or occlusion.

Inability to cross the lesion without unprotected predilation occurred in 12% of filter group patients but in none of the balloon group ($P = .001$). In 5% of the filter group, the lesion could not be crossed despite unprotected predilation. In these cases, the CAS procedure was completed using balloon EPD. The balloon EPD crossed all lesions attempted.

Spasm requiring pharmacologic treatment occurred more frequently in the filter group (12%) than the balloon group (2%, $P = .002$). In all cases, however, the spasm resolved after removal of the EPD and intra-arterial infusion of 100 μg of nitroglycerin through the arterial sheath. It had no apparent clinical consequence.

Filter clogging with no reflow through the ICA was observed in two cases. This required aspiration of the filter basket with an Export catheter (Medtronic). In addition, 100 μg of nitroglycerin was given through the sheath. In both cases, flow was restored across the filter after aspiration of the filter, which allowed safe capture and removal of the filter.

In two cases in the balloon group, the ICA lesion was not initially completely covered, and a second stent was required. This was partly because of the inability to obtain angiographic visualization of the ICA while the balloon EPD is deployed. Additional less frequent complications included prolonged time to remove the filter in three cases and kinking of the balloon EPD before balloon inflation in one case. These had no clinical consequence.

DISCUSSION

Few studies at present compare differences between balloon and filter EPDs. Zahn et al[11] reviewed the outcomes of the Carotid Angioplasty and Stent Registry. In this large series, 553 patients received filter EPDs and 176 received balloon EPDs. The neurologic event rates between the two groups did not differ; however, balloon EPDs were used more frequently in patients with complex or critically narrow stenoses. This study did not compare technical difficulties encountered with these two types of EPDs.

The PercuSurge GuardWire balloon occlusion wire has had widespread clinical use even though it does not have FDA approval for use in CAS. It has been shown to reduce myocardial ischemic events after angioplasty of coronary saphenous vein grafts and has FDA approval for this indication.[12] Henry et al[13] reported a stroke rate of 4% in patients undergoing CAS with this embolization protection device. These authors found that 5% of patients did not tolerate ICA balloon occlusion.

The MAVERIC (Evaluation of the Medtronic AVE Self-Expanding Carotid Stent System in the Treatment of Carotid Stenosis) trial, an open label trial utilizing the GuardWire balloon occlusion EPD and Exponent stent (Medtronic), reported a combined cardiac and neurologic event rate of 5.4% in high risk patients.[14] Theoretical advantages of this device include greater ease of crossing critically stenotic or tortuous lesions because of the low crossing profile. The compliant balloon is mounted on a hollow 0.014-inch wire with a crossing profile of 3.0F (0.036-inch). In addition to low profile, the balloon EPD is more flexible and allows for increased trackability.

Theoretical disadvantages of this device include concerns that patients with severe contralateral carotid disease may not neurologically tolerate ICA occlusion. This device is also more complex to deploy compared with filters. The findings from the present study support many of these contentions. The balloon EPD crossed all lesions attempted without the need for unprotected predilation. However, 10% of patients did not tolerate initial balloon occlusion. In these cases, the procedure could usually be completed by deflating the balloon, transiently raising the mean systemic blood pressure, and then reinflating the balloon. No patient-specific or anatomic-specific predictors of balloon occlusion intolerance were identified; however, contralateral intracranial anatomy was not routinely assessed either before or during the CAS procedure.

Filter EPDs are generally thought to be simpler to use and offer the anticipated advantage that neurologic compromise is less likely than during use of balloon EPDs. For these reasons, at least seven different filter designs have currently completed or are in clinical trials. At present, only two filter systems are FDA-approved for CAS, the Accunet and Emboshield (Abbott, Abbott Park, Ill), although approval of several additional filter systems is likely in the near future.[15]

Numerous clinical trials of various filter EPDs have been completed. These results, summarized elsewhere, have shown a combined 30-day cardiovascular adverse event rate of 6% to 12%.[16] These filter EPDs generally have larger crossing profiles than balloon EPDs, from 3.4F to 3.9F (0.045 to 0.050 inches). In addition, filter EPDs have an abrupt change between the floppy distal wire and the

filter basket that can adversely affect trackability. These potential drawbacks may decrease the ability for filter EPDs to cross critically stenotic or tortuous carotid bifurcation stenoses.

The results of the present study confirm many of the theoretical advantages of the filter EPDs. All patients in whom the filter EPD could be deployed tolerated this without neurologic compromise. In 7% of patients, however, the lesion could not be crossed until unprotected balloon dilation was performed with a 1.5-mm or 2-mm balloon. In two additional patients, the lesion could not be crossed despite predilation, and balloon occlusion was successfully used in these cases to complete CAS.

In addition to the development of neurologic compromise and the inability to cross critically tight stenoses, our study identified less frequent technical issues that appeared to be EPD specific. These included difficulties with accurate stent placement when the balloon EPD was used because of the inability to angiographically visualize the distal extent of the lesion as a result of occluded ICA flow. Placement of a stiff stent over the balloon EPD can alter the geometry of the ICA bifurcation. This is difficult to reassess with angiography because of ICA occlusion during balloon inflation. This required placement of a second ICA stent on two occasions in the present study. In one additional case, the balloon EPD wire was kinked before balloon deployment. This necessitated removal of the EPD and placement of a second EPD. Kinking of the balloon EPD after balloon inflation, although not observed in our experience, would be of much greater concern, since deflation of the balloon could be more difficult.

Filter clogging with embolic debris is an uncommon problem that occurred in two patients in the filter group during the present study. It is mandatory to perform repeat angiography after post-stent balloon dilation before filter removal to identify this problem. In the present study, aspiration of the ICA and filter restored flow through the filter and allowed safe removal. In two cases, the long floppy portion of the guidewire that extends beyond the filter would have crossed coexistent intracranial disease if it had been used. In these cases, the filter was removed and the procedure was completed with the balloon EPD in which there is a shorter amount of wire that extends beyond the balloon.

Finally, removal of the Guidant filter EPD filter was prolonged in three patients. Removal of the filter was hampered by the inability of the capture catheter to cross the stent. This occurred despite preshaping the catheter tip. Capture of the filter required placing the patient's head in various positions to straighten the stent, external neck compression, or advancing the arterial sheath into the proximal stent.

Technical difficulties were common with both types of EPD but were not correlated with adverse outcomes. The absence of any significant difference, however, could be due to the relatively small numbers of patients in our study.

CONCLUSIONS

EPD-related technical difficulties were encountered, and although they appeared to have no effect on clinical outcome, vascular surgeons need to be prepared to handle these as they arise during CAS. In addition, familiarity with different types of EPDs may allow the surgeon to treat a broader clinical spectrum of patients with CAS. We prefer to use filter devices preferentially in most cases to avoid the 10% incidence of reversible neurologic compromise that occurs with balloon occlusion. However, we prefer balloon occlusion EPDs for critical stenoses that would be more difficult to cross with currently available filter systems without predilation. With such critical stenoses, it is less likely that the patients would not tolerate ICA occlusion. Thus, balloon and filter type EPDs have complimentary advantages and disadvantages that allow selection according to unique patient and lesion characteristics.

AUTHOR CONTRIBUTIONS

Conception and design: RJP, CA, JLC
Analysis and interpretation: RJP, CA, JLC, DW, MF, ER, BN, MW, BZ
Data collection: RJP, CA
Writing the article: RJP, CA
Critical revision of the article: RJP, CA, JLC, DW, MF, ER, BN, MW, BZ
Final approval of the article: RJP, CA, JLC, DW, MF, ER, BN, MW, BZ
Statistical analysis: RJP, CA
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Overall responsibility: RJP

REFERENCES

1. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al; Stenting, Angioplasty with Protection in Patients at High Risk for Endarterectomy investigators. Protected carotid-artery stenting versus endarterectomy in high-risk patients.[see comment]. N Engl J Med 2004;351:1493-501.
2. Ohki T, Marin ML, Lyon RT, Berdejo GL, Soundararajan K, Ohki M, et al. Ex vivo human carotid artery bifurcation stenting: correlation of lesion characteristics with embolic potential. J Vasc Surg 1998;27: 463-71.
3. Alberts MJ. Results of a Multicenter Prospective Randomized Trial of Carotid Artery Stenting vs. Carotid Endarterectomy. Stroke. 2001;32: 325 (abstract).
4. Diethrich EB, Ndiaye M, Reid DB. Stenting in the carotid artery: initial experience in 110 patients. J Endovasc Surg 1996;3:42-62.
5. Roubin GS, Yadav S, Iyer SS, Vitek J. Carotid stent-supported angioplasty: a neurovascular intervention to prevent stroke. Am J Cardiol 1996;78:8-12.
6. Powell RJ, Schermerhorn M, Nolan B, Lenz J, Rzuidlo E, Fillinger M, Walsh D, Wyers M, Zwolak R, Cronenwett JL. Early results of carotid stent placement for treatment of extracranial carotid bifurcation occlusive disease. J Vasc Surg 2003;39:1193-9.
7. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature.[see comment]. Stroke 2003;34:813-9.
8. Ohki T, Parodi J, Veith FJ, Bates M, Bade M, Chang D, et al. Efficacy of a proximal occlusion catheter with reversal of flow in the prevention of embolic events during carotid artery stenting: an experimental analysis. J Vasc Surg 2001;33:504-9.

9. Reimers B. MOMA registry. J Endovasc Ther 2005;12:156-65.
10. Parodi JC, Ferreira LM, Sicard G, La Mura R, Fernandez S. Cerebral protection during carotid stenting using flow reversal. J Vasc Surg 2005;41:416-22.
11. Zahn R, Ischinger T, Mark B, Gass S, Zeymer U, Schmalz W, et al; Arbeitsgemeinschaft Leitende Kardiologische K. Embolic protection devices for carotid artery stenting: is there a difference between filter and distal occlusive devices? J Am Coll Cardiol 2005;45:1769-74.
12. Baim DS, Wahr D, George B, Leon MB, Greenberg J, Cutlip DE, et al. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. Circulation 2002;105:1285-90.
13. Henry M, Polydorou A, Henry I, Hugel M. Carotid angioplasty under cerebral protection with the PercuSurge GuardWire System. Catheter Cardiovasc Interv 2004;61:293-305.
14. Medtronic announces preliminary data from the Maveric I and II Carotid Stent Clinical Trials. www.medtronic.com (2004).
15. Gray WH. The ARCHeR trials: one year results. AHA Scientific Sessions 2004.
16. Goodney P, Schermerhorn M, Powell RJ. Current status of carotid angioplasty stenting. J Vasc Surg 2006;43:406-11.

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